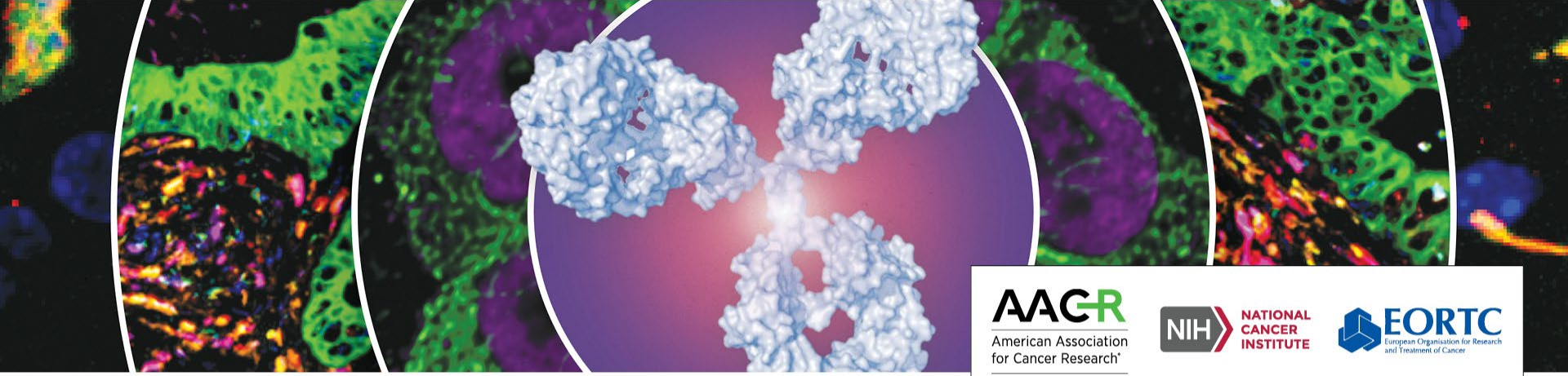

Zenocutuzumab efficacy and safety in advanced *NRG1*+ cholangiocarcinoma: analysis from the phase 2 eNRGy trial

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Disclosure information

Alison M Schram

I have the following relevant financial relationships to disclose:

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ASCO, American Society of Clinical Oncology; CCITLA, Cancer Clinical Investigator Team Leadership Award; CDA, Career Development Award; NCI, National Cancer Institute.

Background

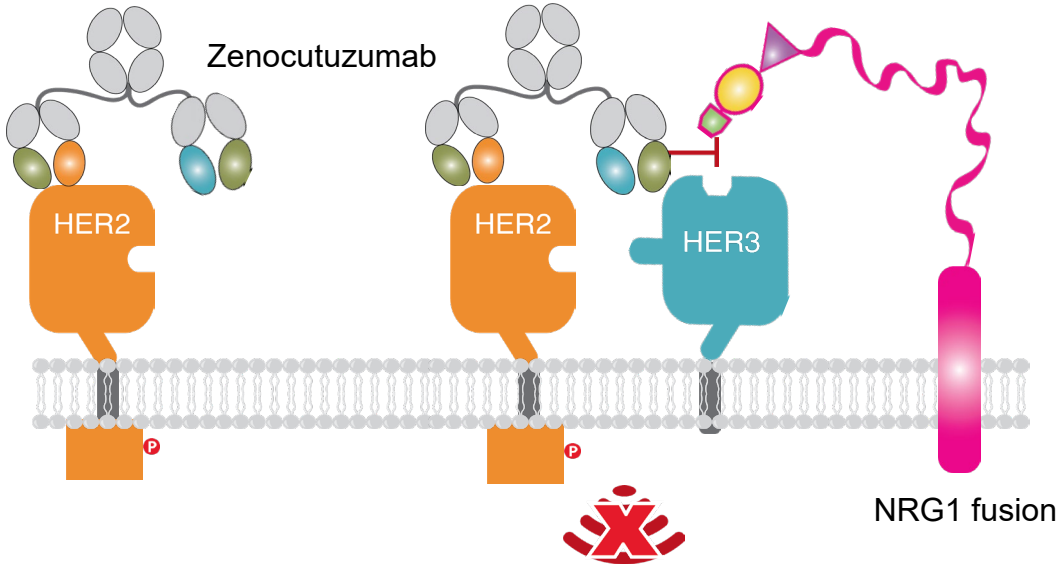
- Cholangiocarcinoma is a rare, aggressive gastrointestinal cancer with a poor prognosis (median survival in advanced disease of ~1 year)[1–4]
- *NRG1* gene fusions are rare oncogenic drivers (prevalence <1% in cholangiocarcinoma)[5–7]
- No approved targeted therapies for *NRG1*+ cholangiocarcinoma exist; cholangiocarcinoma treatment is limited to palliative systemic therapy for metastatic disease[1]

NRG1, neuregulin 1; *NRG1*+, neuregulin 1 gene fusion positive.

1. Banales JM, *et al. Nat Rev Gastroenterol Hepatol.* 2020;17(9):557–588; 2. Valle J, *et al. N Engl J Med.* 2010;362(14):1273–1281; 3. Oh DY, *et al. NEJM Evid.* 2022;1(8):EVIDoa2200015;
4. Kelley RK, *et al. Lancet.* 2023;401(10391):1853–1865; 5. Severson E, *et al. J Mol Diagn.* 2023;25(7):454–466; 6. Laskin J, *et al. Ann Oncol.* 2020;31(12):1693–1703;
7. Jonna S, *et al. Clin Cancer Res.* 2019;25(16):4966–4972.

Zenocutuzumab mechanism of action

- HER2/HER3 IgG1 bispecific antibody
  - Blocks NRG1 fusion binding to HER3
  - Inhibits HER2-HER3 dimerization
  - Induces ADCC
- Received accelerated US FDA approval (Dec 2024) for previously treated, advanced *NRG1*+ NSCLC and PDAC[1]



ADCC, antibody-dependent cellular cytotoxicity; FDA, Food and Drug Administration; HER, human epidermal growth factor receptor; IgG, immunoglobulin G; *NRG*, neuregulin 1; *NRG1+*, neuregulin 1 gene fusion positive; NSCLC, non-small cell lung cancer; PDAC, pancreatic adenocarcinoma.

1. US FDA. FDA grants accelerated approval to zenocutuzumab-zbco for non-small cell lung cancer and pancreatic adenocarcinoma. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zenocutuzumab-zbco-non-small-cell-lung-cancer-and-pancreatic. Accessed September 12, 2025.

eNRGy: Phase 1/2, global, multicenter zenocutuzumab trial[1,2]

eNRGy

NSCLC
PDAC
Other solid tumors, including cholangiocarcinoma

Inclusion criteria

- Age ≥18 years
- Advanced or metastatic solid tumor
- *NRG1* gene fusion*
- Previously treated with or unable to receive standard therapy
- ECOG PS ≤2

Treatment plan

- Zenocutuzumab 750 mg, 2-hour† IV infusion Q2W until PD or unacceptable toxicity
- Tumor assessment Q8W

Enrollment and analysis

Cholangiocarcinoma

Data cutoff date:
April 9, 2025

Patients enrolled (safety analysis subset): n=22

Primary efficacy subset: n=19

- Excluded due to *KRAS* mutation (n=1)
- Excluded due to prior anti-HER3 antibody therapy (n=2)

Endpoints

Primary endpoint

ORR using RECIST v1.1 per investigator assessment

Secondary endpoints

- DOR, CBR, and PFS per investigator and BICR assessment
- Safety‡

**NRG1* gene fusion status was determined by NGS. †To mitigate potential IRRs, the initial infusion was administered over a period of 4 hours and patients received premedication with antipyretics, antihistamines, and glucocorticoids. ‡Adverse events were assessed from the date of the first zenocutuzumab dose up to 30 days after the last dose and graded using CTCAE v4.03. BICR, blinded independent central review; CBR, clinical benefit rate; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER, human epidermal growth factor receptor; IRR, infusion-related reaction; IV, intravenous; *KRAS*, Kirsten rat sarcoma virus; NGS, next-generation sequencing; *NRG1*, neuregulin 1; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival; Q2W, every 2 weeks; Q8W, every 8 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Schram AM, *et al. N Engl J Med*. 2025;392(6):566–576; 2. ClinicalTrials.gov. NCT02912949. https://clinicaltrials.gov/study/NCT02912949. Accessed September 12, 2025.

Patient demographics

Demographics

Characteristic	Safety analysis set (N=22)
Age, years, median (range)	57.5 (23–82)
Male, n (%)	10 (45)
ECOG PS, n (%)	
0	14 (63)
1	7 (32)
2	1 (5)
Anatomical location, n (%)	
Intrahepatic	18 (82)
Unknown	4 (18)
Stage at screening, n (%)	
IIIB	1 (5)
IV	21 (95)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Treatment history

Diagnosis and prior therapy

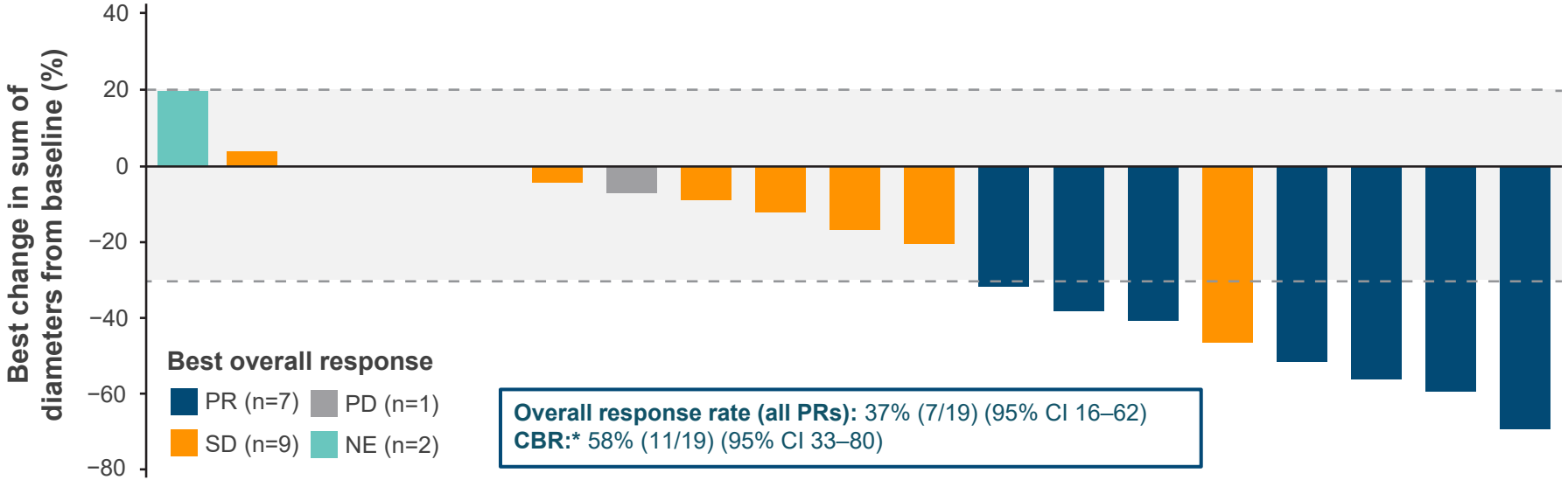
Diagnosis and prior therapy	Primary efficacy set (N=19)
Time since metastatic diagnosis, months, median (range)	9.3 (1.6–34.2)
Patients receiving prior systemic therapy, n (%)	17 (89)
Type of prior therapy, n (%)	
Chemotherapy	16 (84)
Immunotherapy	3 (16)
Anti-VEGF therapy	1 (5)
Transarterial chemoembolization	1 (5)

Number of prior therapy regimens

Number of prior therapy regimens	Primary efficacy set (N=19)
Prior systemic therapy regimens, n, median (range)	1 (0–4)
Prior systemic therapy regimens, n (%)	
0	2 (11)
1	9 (47)
2	5 (26)
3	1 (5)
4	2 (11)

VEGF, vascular endothelial growth factor.

Best overall response

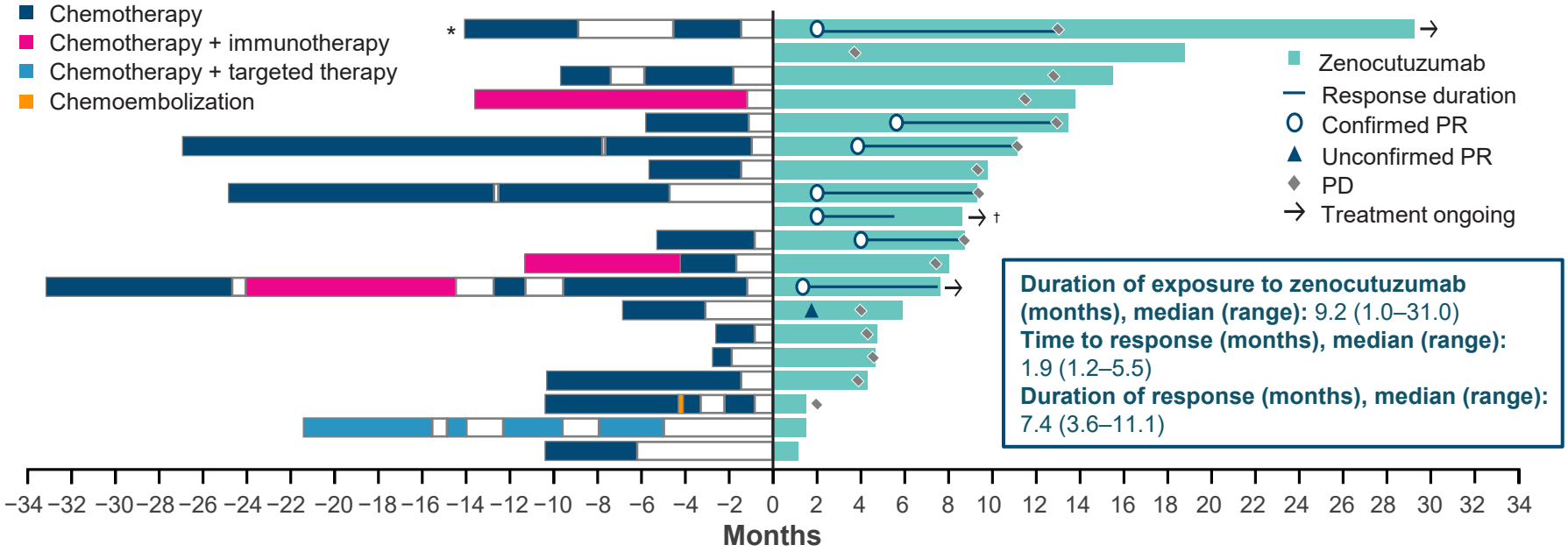


Primary efficacy set, n=19.
*Defined as the proportion of patients who experienced a CR or PR or who had SD for ≥24 weeks.
CBR, clinical benefit rate; CI, confidence interval; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Treatment exposure and response

Prior treatment exposure

Study treatment exposure and response

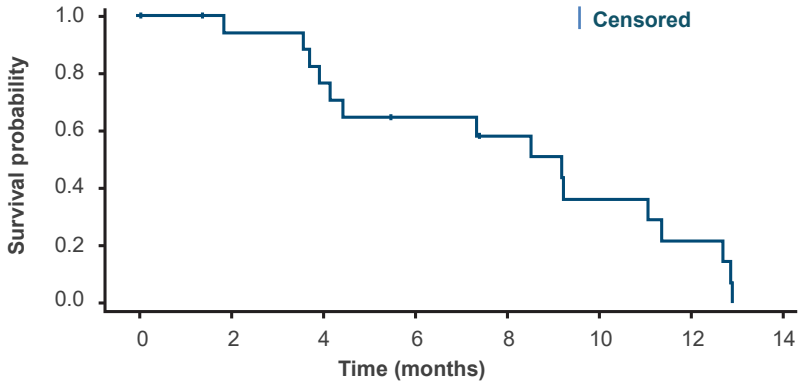


Duration of exposure to zenocutuzumab (months), median (range): 9.2 (1.0–31.0)
Time to response (months), median (range): 1.9 (1.2–5.5)
Duration of response (months), median (range): 7.4 (3.6–11.1)

Primary efficacy set, n=19.
*This patient had two surgical resections with adjuvant chemotherapy given each time. †Response data missing due to data entry error; however, continued PR has been confirmed with the investigator.
PD, progressive disease; PR, partial response.

Progression-free and overall survival

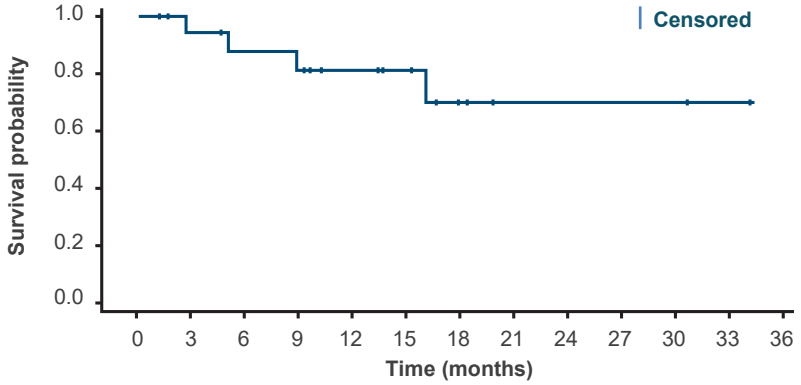
Kaplan–Meier of PFS



Patients at risk, n	19	16	13	10	8	5	3	0

PFS, months, median (95% CI): 9.2 (3.9–11.4)

Kaplan–Meier of OS



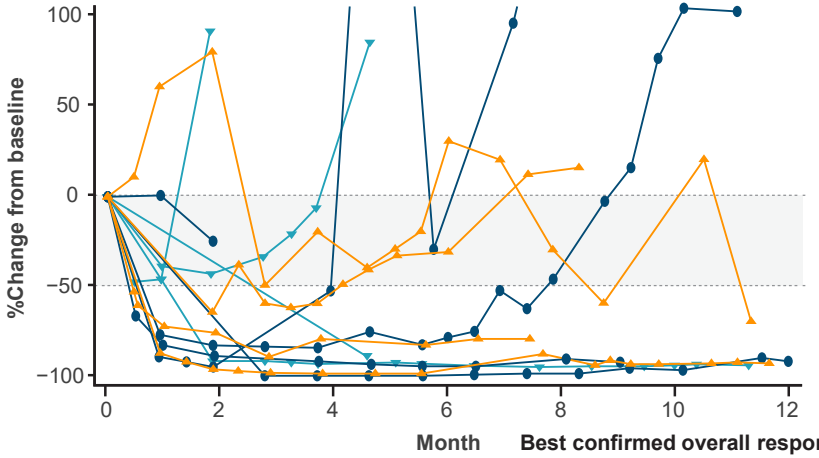
Patients at risk, n	19	16	14	13	10	8	4	2	2	2	2	1	0

Duration of follow-up, months, median (range): 15.2 (1.2–34.1)
OS, months, median (95% CI): NE (16.1–NE)

Primary efficacy set, n=19.
CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival.

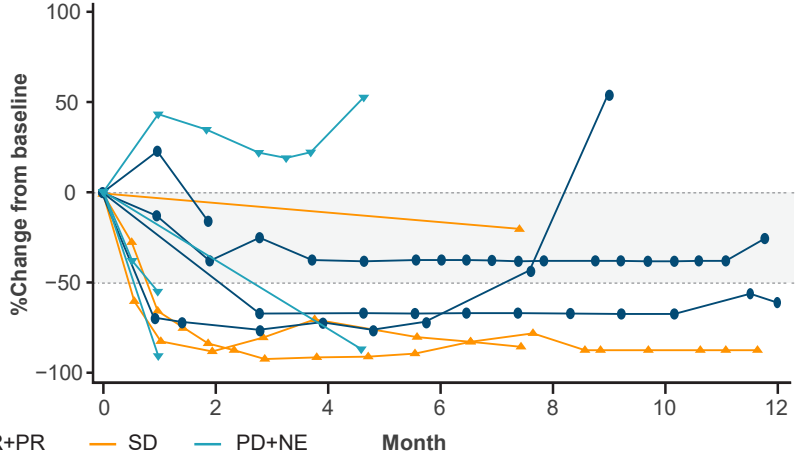
Change in biomarkers

Percent change from baseline in CA19-9



CA19-9 decline: 100% (16/16) of CA19-9–evaluable patients
% of patients with 50% reduction: 68.8% (11/16)
Median time to first 50% reduction: 1.0 month

Percent change from baseline in CEA



% of patients with 50% reduction: 63.6% (7/11)
Median time to first 50% reduction: 1.0 month

Best confirmed overall response — CR+PR — SD — PD+NE

Biomarker-evaluable patients defined as those with baseline and post-baseline measurements of CA19-9 (n=16) and CEA (n=11). Data points that go above the axis of these figures are censored.
CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Safety analysis

Safety summary

Adverse events	Safety analysis set, n (%) (N=22)	
Patients with ≥1 TEAE	21 (95)	
Patients with ≥1 TRAE	13 (59)	
Patients with Grade ≥3 TRAE	1* (5)	
Patients with ≥1 serious TEAE	5† (23)	
	All grades	Grade 3–4
Infusion-related reactions	2 (9)	0 (0)

TEAEs occurring in ≥20% of patients

Adverse events	Safety analysis set, n (%) (N=22)	
TEAEs occurring in ≥20% of patients	All grades	Grade 3–4
Anemia	10 (45)	3 (14)
Diarrhea	9 (41)	0 (0)
Hypomagnesemia	6 (27)	2 (9)
Abdominal pain	6 (27)	1 (5)
Cough	6 (27)	0 (0)
Fatigue	6 (27)	0 (0)
Nausea	6 (27)	0 (0)
ALT increased	5 (23)	1 (5)
GGT increased	2 (9)‡	2 (9)

*Grade ≥3 treatment-related anemia was reported in 1 patient (5%). This did not lead to treatment discontinuation. †None were considered related to study drug. All were Grade ≤3 in severity.
‡GGT increase occurred in <20% of patients; however, they are included here as both events were Grade ≥3. Neither event was treatment-related.
ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Conclusions

- Zenocutuzumab demonstrated meaningful clinical activity in patients with *NRG1+* cholangiocarcinoma
  - ORR of 37% and CBR* of 58%
  - Median time to response of 1.9 months; median duration of response of 7.4 months
  - CA19-9 declined in 100% of CA19-9–evaluable patients (16/16) including >50% reduction in 69% (11/16)
- Zenocutuzumab had a favorable safety profile in this cohort
  - Most AEs were Grade 1 or 2 and were manageable
  - Treatment-related AEs occurred in 13 patients (59%); none led to study discontinuation
- Results are consistent with those observed with zenocutuzumab in patients with other *NRG1+* solid tumors, including NSCLC and PDAC[1]

*Defined as the proportion of patients who had a complete or partial response or who had stable disease for ≥24 weeks.
AE, adverse event; CA19-9, carbohydrate antigen 19-9; CBR, clinical benefit rate; *NRG1+,* neuregulin 1 gene fusion positive; NSCLC, non-small cell lung cancer; ORR, overall response rate; PDAC, pancreatic adenocarcinoma.

1. Schram AM, et al. *N Engl J Med.* 2025;392(6):566–576.

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